## REMARKS

Applicants respectfully request reconsideration. Claims 32-53 were previously pending in this application. Claims 48-53 were previously withdrawn from consideration. No claims have been amended herein. As a result, claims 32-47 are still pending for examination with claim 32 being an independent claim. No new matter has been added.

### Interview Summary

Applicants thank Examiner Falk for the courtesy of a telephone interview with Applicants' representatives on Tuesday, November 25, 2008. During the interview several arguments for overcoming the rejections under 35 U.S.C. §112 were put forth by Applicants' representatives and discussed with Examiner Falk. In particular, Applicants' representatives provided further arguments that the specification as filed enables the full scope of HBV antigen, as claimed. The Examiner suggested that data demonstrating an antigen specific immune response to DNA vaccination by intramuscular injection of expression plasmids encoding additional HBV antigens (e.g., core antigens) and in multiple subjects would be helpful in overcoming the rejection. Applicants submit herewith several literature references which describe the use of various HBV antigens, including surface and core antigens, using the methods of the claimed invention for producing antigen specific immune responses in multiple species. Thus, it is believed that the outstanding issues related to the pending claims have been resolved.

### Double Patenting Rejection

Claims 32-47 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,635,624.

Applicants may file a Terminal Disclaimer depending on the claims that are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

**Rejection Under 35 U.S.C. 112**

Claims 32-47 have been rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the methods as claimed, wherein the vector comprises a gene encoding the hepatitis B virus surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in a mammal, does not reasonably provide enablement for the use of a vector encoding any other HBV antigen. Applicants respectfully traverse for at least the following reasons.

The pending claims relate to a method for inducing an antigen specific immune response in a subject. The method involves administering to the subject an expression plasmid vector capable of expressing a hepatitis B virus antigen and including a promoter for the expression of the hepatitis B virus antigen in the subject in an effective amount to induce an antigen specific immune response against the hepatitis B virus antigen. The specification teaches that the hepatitis B antigen may be a structural protein or a regulatory protein. (page 6, lines 7-12). Exemplary HBV antigens are disclosed in the specification and include HBV proteins and portions of proteins (i.e., fragments) such as HBV surface antigens and core antigens (*See*, for example, page 4, line 2; page 5, lines 16-17; and page 6 lines 10-15 of the instant specification). The specification as filed discloses a series of exemplary expression vectors encoding HBV surface antigens (*See*, for example, page 16, lines 5-19) and provides working examples evidencing that intramuscular injection of the expression vectors induces antigen specific immune responses in mice (*See*, for example, page 18, line 8 – page 19, line 22 and figure 8) and in rabbits (*See*, for example, page 19, lines 23-27 and table IV) with antibody levels exceeding 10 mUI/ml, which is the threshold required to provide protection humans (*See*, for example, page 23, lines 26-28). Moreover, using methods well known in the art, the skilled artisan could readily produce expression DNA vectors encoding immunogenic HBV antigens to perform the claimed methods.

Applicants previously presented a full Wands analysis (Office Action Response dated July 22, 2008), and maintain that this analysis demonstrates that the claimed methods were enabled as of the filing date. Nevertheless, the Examiner continues to argue that the specification does not enable the full scope of HBV antigens and, in particular, that HBV antigens other than surface antigens are not enabled across a full scope of subjects. This argument is based primarily on post-filing

references cited to establish the unpredictability in the field following the invention. As discussed in the above-referenced telephone interview, Applicants now present published data demonstrating an antigen specific immune response to DNA vaccination by intramuscular injection of expression plasmid vectors encoding additional HBV antigens (e.g., core antigens) and in multiple subjects to rebut any general teachings of unpredictability regarding the claimed invention.

Post-filing data that follows the teachings of a disclosure to obtain a successful result can be used as evidence in establishing that "the disclosure was in fact enabling when filed"(See In re Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995)). Since the time the instant invention was filed, numerous reports have been published using the methods of the pending claims which demonstrate that intramuscular injection of expression plasmid vectors encoding HBV antigens (including surface and core antigens) induce specific immune responses in a variety of species (including mice, ducks, woodchucks, chimpanzees, and humans). A full range of immune responses have been described including humoral and cellular responses and protection against viral challenge (i.e., a protective immune response). Applicants' present several of these reports below. Each report uses the methods set forth in the instant invention and, thus, is evidence that the skilled artisan, following the methods of the disclosure could have practiced the claimed invention at the time of filing.

Mouse models of Hepatitis B Virus (HBV) have been a mainstay for many key advances in understanding HBV infection and developing treatments that fight the infection in humans. In mice, intramuscular injection of plasmid DNA vectors expressing HBV surface antigens induces antigen-specific antibody production at levels greater that 10 mUI/ml that persists for several months without boosting. (Davis H.L., et al., Hum. Mol. Genet. 2, 1847-1851 (1993) and Mancini M., et al., J. Biotechnol. 1996; 44:47-57). In addition, Lee Y.-S. et al., demonstrate that intramuscular injection of mice with an expression plasmid vector encoding Hepatitis B core antigens obtained from chronic active hepatitis patients results in a strong, specific antibody (Table 1) and cytotoxic lymphocyte (Figures 6 and 7) response. (Lee, Y.-S., et al., Immunology Letters 78 (2001) 13-20.) Similarly, Kuhrober A, et al., have shown that intramuscular injection of expression plasmid vectors encoding Hepatitis B core and 'e' antigens stimulate potent and specific antibody production and cytotoxic lymphocyte responses in mice. (Kuhrober A., et al., Int. Immunology, Vol. 9, No. 8 pp. 1203-1212 (1997).)

In woodchucks, Woodchuck Hepatitis Virus (WHV) causes acute self-limiting and chronic infection similar to the effects of HBV in humans, which is accompanied by a specific humoral response to WHV surface and core antigens. (Lu M. et al., Journal of Virology, Jan. 1999, p. 281-289). Lu M et. al. show that intramuscular injection of woodchucks with a plasmid encoding either WHV surface or core antigens induces a specific immune response and controls subsequent WHV infection in challenge experiments (See, Lu M et al., e.g., Table 2 and Figure 7).

Duck Hepatitis B Virus is closely related to HBV and has been used to study viral neutralization mechanisms in its natural host, the Pekin duck. (Triyatni et al., Journal of Virology, Jan. 1998, p84-94). Triyatni et al., show that intramuscular injection of Pekin ducks with DNA vaccines coding for DHBV pre-S/S and S proteins results in the production of high titers of anti-DHBs antibodies (See, Triyatni et al., Figures 3 and 4) and protects the ducks from subsequent viral challenge, as evidenced by clearance of DHBV inoculum from the bloodstream and reduction of DHBsAg in liver (See, Triyatni et al., Figures 5 and 6).

Chimpanzees are similar to humans in their susceptibility to HBV infection and in the antibody titers required for protection. Moreover, HBV surface and core antigens are immunogenic in chimpanzees and confer protection against HBV challenge. (Davis, H.L. et al., Proc. Natl. Acad. Sci. USA Vol. 93, pp. 7213-7218, July 1996). Davis, H.L. et al., have shown that DNA vaccination of chimpanzees against HBV by intramuscular injection of expression plasmid vector (pCMV-S2.S) encoding the small and middle HBV envelope proteins (referred to as *HBsAg*) induced a specific humoral response and helper T-cell response, and produced antibodies titers well above the critical protective level set by the Center for Disease Control for Humans. (See Davis, H.L. et al., at page 7126.) Similarly, Prince AM et al., showed that DNA vaccination of newborn chimpanzees by intramuscular injection of plasmid encoding HBV S and pre-S2 antigens induced a specific humoral response and protection against HBV challenge. (Prince AM et al., Vaccine 1997, Vol. 15, No. 8, pp. 916-919).

Recently, phase I clinical trials in patients with chronic active viral hepatitis have revealed that intramuscular injections of a DNA vaccine encoding HBV surface antigens are well tolerated and induce specific T-cell responses (See, e.g., Table 2, Mancini-Bourgine, M., et al., Hepatology, (2004) 40:874-882 and Figure 4, Mancini-Bourgine, M., et al., Vaccine 24 (2006) 4482-4489.)

Notably, these studies employed pCMV-S2.S (encoding *HBsAg*) which induces specific immune responses in both mice (Michel ML, et al., Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5307-11.) and chimpanzees (*See above*, Davis, H.L. et al., (1996)) and, thus, demonstrates predictability of HBV antigens across subjects.

In summary, the post-filing art cited above demonstrates that, in accordance with the methods of the claimed invention and the teachings of the supporting specification, intramuscular injection of expression plasmid vectors encoding a range of HBV antigens, which include both surface and core antigens, induce a protective immune response across a range of subjects. Based upon the foregoing, Applicants respectfully submit that the claimed invention was enabled as of the filing date of the application. Accordingly, withdrawal of the rejection of claims 32-47 under 35 U.S.C. § 112 is respectfully requested.

## CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. O0277.70001US00.

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Respectfully submitted,

By _____

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000